



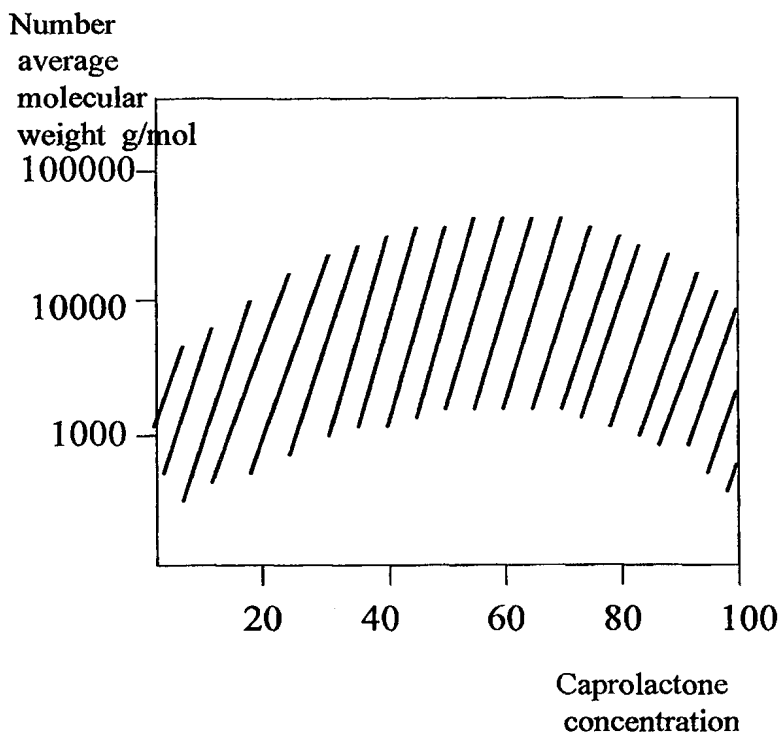
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61L 31/00, 27/00, A61K 6/087		A1	(11) International Publication Number: WO 98/26814
			(43) International Publication Date: 25 June 1998 (25.06.98)
(21) International Application Number: PCT/FI97/00786 (22) International Filing Date: 16 December 1997 (16.12.97) (30) Priority Data: 965067 17 December 1996 (17.12.96) FI (71) Applicant (for all designated States except US): JVS-POLYMERS OY [FI/FI]; Innopoli B463, Tekni- ikantie 12, FIN-02150 Espoo (FI). (72) Inventors; and (75) Inventors/Applicants (for US only): SEPPÄLÄ, Jukka [FI/FI]; Mäkipellontie 18C, FIN-00320 Helsinki (FI). ORAVA, Petri [FI/FI]; Leppäkertuntie 3C30, FIN-02120 Espoo (FI). (74) Agent: SEPPÄLÄ, Jukka; Mäkipellontie 18C, FIN-00320 Helsinki (FI).		(81) Designated States: US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i> <i>With amended claims.</i>	

(54) Title: PLASTICIZABLE IMPLANT MATERIAL

(57) Abstract

The invention is related to an implanting or filling method in connection with clinical treatments, and to biocompatible and at a controlled rate biodegradable synthetic polymer materials used in connection with the same. The materials are copolymers of derivatives of organic hydroxy acids, such as lactides and lactones, having a melting temperature adjusted to be most preferably 6 – 12 °C above the body temperature through selection of monomer composition and preparation parameters. Thus said material in a molten state or as plasticized can be, through injection or using a suitable heated press, transferred to its target area and there shaped before it solidifies to a solid plastic, a wax or a rubbery material. The method can be utilized in medical applications aiming at controlled release of drugs or other active agents when the material acts as a matrix, as well as in surgery and dentistry for different kinds of treatments of tissue damages.



FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakistan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

PLASTICIZABLE IMPLANT MATERIAL

- During the last years in the biomedical applications synthetic implant materials have been taken into use to an ever-increasing degree. Biomaterial is defined to be a synthetic structural material whose aim is to interact with the biological system, and to replace, to treat, promote healing and renewal of and to join tissue, organs or some function of the body. Applications of these materials are reviewed in a publication edited by Höcker *et al.* (Macromolecular Symposia, vol. 103, January 1996, Klee, D., Severich, B., Höcker, H., pp. 19 - 29). Among the most important present and future applications are fixation materials of different types for bone fracture treatment which can be used for manufacturing screws, nails or rods for the above mentioned application, just to mention an example. These materials can be either non-biodegradable ones, e.g., metals or metal alloys, or polymeric materials degradable at a controlled rate in the body.
- 15 The most widely used biodegradable materials are high molecular weight lactide homopolymers, and lactide copolymers with, for example, glycolide. Useful parts or products are processed from these materials with processing methods for thermoplastics known in polymer technology, such as injection molding, hot pressing or extrusion.
- 20 Dentistry is well familiar with polymeric materials, too. Typical polymeric dental filling materials are chemically (for example, photochemically) curable plastics based on methyl methacrylate, dimethyl acrylate and their derivatives.

- Fixation bone cements for orthopedic hip prostheses are also based on monomer combinations methacrylate type. In these applications the curing is based on redox initiated free radical polymerization, and on thus accomplished cross-linking and network formation.
- 25

- The methacrylate based implant materials are, however, neither biodegradable nor biocompatible to any particular extent, as Dr. Heikkilä reports in his dissertation (Annales Universitatis Turkuensis Ser. D: Medica-Odontologica, tom. 240, 23.8. 1996,
- 30

Turku/Finland, Heikkilä, J., Bioactive glass as a bone substitute in experimental and clinical bone defects, pp. 1-97, especially on p. 30).

In the use of methacrylate based implant materials further problems are caused by the exposition of personnel to volatile compounds, and the heat released during the reaction which may lead to an excessive local temperature increase, and to tissue damages as a consequence .

Another application for synthetic implant materials is controlled release of drugs or other bioactive substances when the idea is that the potent agent is released at a controlled rate from the polymeric matrix. As an example of this kind of application one can mention Norplant, a product brand and a trade mark of Leiras Co., which is based on a non-degradable polymeric material. A definitely formed device is implanted into the body by a surgical operation, and it is removed therefrom in a similar manner after a defined time when the active component has been released and diffused to the body.

Specific needs for development in the present state of the art are connected to the following areas:

20 Biocompatibility

If the material is not biocompatible it may induce tissue inflammation, unwanted cell growth, or rejection. Biocompatibilities of the presently used bone cements based for the most part on poly(methyl methacrylate) are unsatisfactory. This causes a certain risk of loosening of the hip prosthesis even in the case that there exists connective tissue formation between the polymeric material and bone tissue. A better biocompatibility would be a significant benefit for these materials.

Bioactivity

A bioactive implant material makes possible an active interaction between the tissue and the implant. As an example can be taken a mechanism by which the tissue is enabled to

reconstruct into the implanted material while the implanted material itself is gradually removed due to biodegradation. Heimke, G. and Griss, P. have in their publication (Tissue interactions to bone replacement materials, in Bioceramics of calcium phosphate, de Groot, K. (ed.), 1983, CRC Press, Boca Raton FL, pp. 79-97) characterized the concept of bioactivity, and have been cited by Heikkilä in his publication (Fig. 1 in the publication cited on page 1 where a) bioincompatible materials, b) bioinert but by the interface biocompatible materials, and c) bioactive and biocompatible materials are presented schematically. In the case a) the implant is tolerated but no connection with bone is formed, in the case b) intimate contact without bone bonding occurs at the interface whereas in the case c) both intimate contact with chemical bone bonding and gradual transformation between bone and implant material will result).

Bioactive materials have scarcely been reported in the literature. Especially in the case of bone cements bioactivity would be desirable and a significant benefit.

Controlled biodegradation

Depending on the application and purpose of implant materials, they are expected to have either long lasting durability or controlled degradability in the body at a predetermined rate to harmless degradation products. The wanted degradation rate is depending substantially on the renewal rate of the tissue. In the case of bone tissue, it may be case of several months, or even of a time span in the range of half an year to one year.

In the case of controlled drug delivery it is crucial what is the desired rate of release of the active ingredient from the biodegradable matrix. When the potent ingredient release is based on matrix degradation the rate of matrix degradation determines the release rate of the drug. When active agent is released from the matrix through diffusion, degradation of the matrix shall happen mainly only after the release of the active agent.

Industrial hygienic aspects

The materials in continuous clinical use have to be safe to the users in a sense of work safety and hygiene. This is a severe drawback with the present bone cements and dental filling materials which are based on methacrylates.

Controlled mechanical properties

The mechanical properties required from implant materials are depending on the application. With bone implants usually a compression strength of at least 50 Mpa is necessary, as well as bending strength and tensile strength values which are at the level of those of bone. On the other hand, even in the bone applications, in case of bone grafting by filling of fractures and cavities, one can fairly well apply implant materials of lower strength if only the use properties, mouldability, biocompatibility, and possible biodegradability are at an optimum level.

In connection with soft tissue the requirements, on the other hand, are elasticity, flexibility and softness.

20 Plasticizability and hardening thereafter

The today used polymeric implant materials are either pieces of definite shape, i.e., processed before implanting to the final form using methods known in the plastics technology (as an example one can mention biodegradable bone nails based on polylactide, e.g., trade name Biofix), or bone cements based on methacrylate which typically have no biodegradability and lack bioactivity but as monomers, or as a blend of monomers, can be shaped in the target according to the needs, and can be hardened thereafter.

In surgery there would be plenty of applications for plasticizable, and afterwards to solid curable biodegradable polymeric materials. Then the idea is, that the material is plastic in connection to the surgical operation, and can be shaped according to the target's shapes or can be forced to penetrate even into small cavities, fractures and pores. Thereafter it again

reversibly becomes solid, mechanically tough material which, however, has the property of controlled degradation. Thus plasticizable material can then be of the type of wax, plastic or rubber.

- 5 Better biocompatibility, bioactivity and wished mechanical properties as combined to the mouldability in the target and hardening occurring thereafter are properties which before the present invention have not been known in the state of the art.

Applicability to the matrix of bioactive components

10

As examples of a bioactive active agent in an implant material can be mentioned different drugs, hormones or components activating tissue growth, such as hydroxyapatite in connection with bone tissue, and certain proteins.

- 15 The matrix has to be such a material that the appropriate hormones can be easily blended with it to form a homogeneous mixture. Especially the upper temperature in this process is often limited because many drugs and hormones are heat sensitive.

Easiness in application (usability and transferability to the target)

20

The implant material is placed to the target in connection to a clinical situation, e.g., in connecton to an operation. Then the applicability and the mouldability of the material has to be easy: it must be possible to, for example, inject it, or to place it with a special press, to the target, and its hardening has to have a certain induction period during which the material can be shaped. On the other hand, one has to take into account that the possible drug present and/or the contact with tissue do not allow use of methods where the temperature even for a short period exceeds the typical upper limit of 55 °C. The invention now present brings a novel solution which significantly improves applicability of biodegradable implants, for example, in regenerating surgery and in long lasting drug
30 therapy.

The description of the invention

In comparison with the present state of the art, it has been possible according to the present invention surprisingly to achieve such a method which brings a significant improvement to it and opens up new possibilities in the use of body implantable polymeric materials. More specifically it has been possible to find such a composition of materials and a method, which enables the combination of several of the important properties in an exceptionally beneficial way from many applications' point of view. Below the invention's characteristic features are explained more in detail through examples which describe one successful way of its implementation .

The developed material is based on as such known structural units used in syntheses of polymeric biomaterials, and on structural units derived from capronic acid. Structural units derived from lactic acid can be, in addition to lactic acid itself, L- , D-, and DL-lactide units. Structural units derived from capronic acid can be, e.g., ϵ -caprolactone. In addition as structural units can be organic carbonates, like trimethylenecarbonate.

Lactones are cyclic esters based on hydroxyacids. Some of the most common lactones are L-lactide, DL-lactide, D-lactide and ϵ -caprolactone. With these to the same group of cyclic monomers can also be included cyclic carbonates, like trimethylenecarbonate.

The polymerization of lactones and cyclic carbonates can be carried out, as is well known, through catalytic ring opening polymerization. The catalyst used is typically some organometallic compound like tin(II)octoate (in other words stannous-2-ethylhexenoate), or trimethylaluminium.

The molecular weight control in this type of polymerization is based on the optimal selection of polymerization temperature and time, and it is possible also using so called initiator compounds, of which typical are multifunctional alcohols, e.g., glycerol. During the polymerization the polymer chains will start to grow from the -OH groups so that the molecular weight will be the lower the more initiator is present. By choosing the structure of the multifunctional alcohol the shape of the forming molecule can be affected. So, for

example, glycerol forms a comb-like and pentaerythritol a star-shaped molecular structure, respectively.

The ring-opening polymerization of lactones is described, for example, in the following publication: Ylikangas, I., The polymerization of ϵ -caprolactone with stannous catalysts, Polymer Technology Publication Series No. 15, Helsinki University of Technology, 1993, 1-23.

Thus it is as such known that by using the above mentioned structural units one can form a biodegradable polymeric material which has either plastic-like or rubbery properties but in the present invention the structural units are used in a special way to achieve a biodegradable polymeric material which melts within a certain narrow temperature range and which, on the other hand, is either a mechanically tough plastic, a wax or a rubbery material below its melting temperature. In respect of implant application it is important that the material melts or plasticizes at a temperature which is somewhere 3 - 12 °C above the body temperature, and becomes again a solid material at a temperature still above the body temperature. The melting and plasticization temperature of the material must, of course, not be too high in respect to the body temperature, taking into account the above described temperature resistance of tissue and of drug-like active agents. When melting or plasticizing the material according to the invention becomes a viscose mass or fluid which can be shaped, injected or otherwise used to fill hollows, fractures and cavities as well as to replace different kinds of tissue defects, as in bone grafting.

In the present invention it has become possible to adjust the temperature at which the material becomes plastic to within the temperature range of 42 - 55 °C, or it can be adjusted to any temperature around this temperature range as well. The melting temperature of the material can be checked by means of measurements of enthalpy changes, using differential scanning calorimetry (DSC) as the method.

The control of the melting temperature of a polymeric material according to the invention is based on one hand on the specific monomer ratio selection in the starting materials, and, on the other hand, on the specific control of the molecular weight in the copolymerization.

Both factors together namely affect the melting temperature of the copolymer, hence only certain combinations of them bring about the wished result. Figure 1 is a graphical presentation the combinations of monomer compositions and average molecular weights for the L-lactide/caprolactone copolymers which produce a suitable melting temperature for implant use, indicated by points falling within the shaded area between curves in the monomer molar ratio versus molecular weight coordination.

In several applications it is wanted that the implanted material is degradable in a controlled manner, or vice versa mechanically stable at least for a certain period of time. The first stage in biodegradation of the materials according to the present invention is hydrolysis which splits polymer chains to shorter segments until the molecular size is at a level where the own enzymatic functions of the body can convert the degradation products to compounds which are natural in the body.

The hydrophilic character of the polymer is an essential parameter affecting the degradation rate. Thus in copolymers of the present invention it is possible to control hydrolytic degradation rate through control of monomer composition, and so also hydrophilic character, which according to what has been presented above directly affects the degradation rate of the material in the body. One has to note, however, that the exact rate of the degradation in the body depends on the end use, and has to be always investigated case by case. Figure 2 indicates the dependence between the hydrolysis rate and monomer composition in the L-lactide / ϵ -caprolactone copolymers prepared in the examples.

An essential feature of the invention is that if the composition of the material comprises only or for the most part ϵ -caprolactone, the rest being L-lactide, DL-lactide, D-lactide or trimethyl carbonate, the polymer is almost stable in the body, or degrades very slowly, typically during several years. Through selection of the monomer composition keeping this in mind, and through adjusting the molecular weight of the forming polymer by controlling the polymerization parameters, one can get benefit from the well-known biocompatibility and bioactivity of poly(hydroxy acid)s. On the other hand, a waxy version of the copolymers according to the invention can be made to degrade even really fast, just by

controlling both average molecular weight and monomer composition as described above. In that case the degradation rate in the body is typically from some days to some weeks.

5 A material according to the invention is in a molten state, i.e., while being at a temperature exceeding 37 °C, preferably within a temperature range from 42 to 55 °C, and most preferably within a temperature range from 43 to 48 °C, a plastic mass or a viscous fluid. This makes it possible to shape the material by hand or by using specific tools to a desired shape to meet the needs of the target, or alternatively makes it possible that the material can, by different transportation methods, be used to fill different and variably shaped
10 spaces, hollows, cavities and fractures numerous existing in surgery, dentistry and medicine.

Especially advantageous in the invention is an unexpected observation that the plasticizable material according to the invention can above its melting temperature be in such a state that
15 it can be applied to the target using a specific press, the schematic drawing of which is presented in Figure 3. Said press essentially consists of a heated cylinder 3, a die 4 (which can be of different kinds according to the needs of the end uses), a piston 5, trigger 2, and a press mechanism 8. The temperature of the cylinder 3 can be regulated at a desired level by a thermostat so that the implantable material is either in a molten state or in a
20 plasticized state inside the cylinder in front of the piston 5, and thus it can be transferred using the press device through the die to the target area. Because the temperature of the molten or plasticized polymeric material is higher than the body temperature but in any case such that there is no danger of tissue damage, the implant material can be transferred directly to the target area where it solidifies when cooling down.

25 Advantages of the method according to the invention are the simplicity for the user, e.g., for the surgeon, hygienicity because the implant material is all the time in a closed chamber, and the point that there are no volatile components utilized in the method (an advantage in respect of industrial hygiene and working safety), and further that there is no
30 heat generation in connection with the solidification (as usually is the case in the solidification of bone cements) and the risk of tissue damages can thus be avoided. As an additional benefit one can mention that by using differently shaped longer dies 2 it

becomes possible to inject the mass to narrow, deep and variously shaped channels to their very end or to their deepest points, to fractures, to cavities and the like as target areas.

Another preferred embodiment of the implantation method according to the invention is the use of such a device which does not contain any specific piston, but the piston 5 is replaced with a rod made up of polymeric material according to the invention which penetrates through the unheated part of the cylinder to the heated part where it melts or plasticizes. The feeding mechanism 8 pushes the rod into the cylinder, and correspondingly the molten or plasticized polymeric material is extruded out through the die 4.

Still one advantageous method to implantate according to the invention is the one where the temperature of the cylinder 3 is raised above one hundred degrees centigrade and is held there for the time required for completing heat sterilization. In this case any separate sterilization is not needed, and the sterilized material remains in its closed space sterile and ready for use. Naturally this form of implantation can be applied provided that there are no heat sensitive active agents, for example drugs, present as blend components. After the sterilization treatment the material is allowed to cool down to the temperature range of 37 - 55 °C so that it remains both sterile and in a molten or plasticized state for the implanting.

One specific way of implantation is the one where the polymer according to the invention is produced in a way that its melt viscosity is low enough to allow its injection to the target area with a suitable injection syringe. In this case the polymeric material when cooled down to its solid state at the body temperature is a waxy material.

The implant material according to the present invention can be applied in a way that the material forms a matrix in the controlled release of drugs, or it forms a matrix in blends containing bioactive inorganic materials where the bioactive component can be selected from the group including, for example, hydroxyapatite, a filler based on coral, bone allocrafts or its particles, titanium particles and carbon fibers, just to mention some. In this form of application the blend component can, of course, also be soluble to the polymeric matrix, as is the case in connection with the most drugs. On the other hand, the solid components in the mixtures may be platelets or fibrous particles so that the composition is

comparable to the polymer composites, and in which case the blend component essentially improves mechanical properties. A special advantage is achieved in the aspect that the use of a biodegradable polymeric matrix yields adhesion between particles, plasticizability, ease of processing, and improved biocompatibility to this kind of materials containing solid particles.

In connection with drugs, hormones, or other corresponding active agents, the method according to the invention enables the controlled release and targeted location to the body, for example, in connection with an operation, or by injecting.

Both composite materials containing solid fillers and/or reinforcements and blends containing soluble components can be located according to the invention, for example, as is presented in figure 3, easily and safely as a plastic mass or a viscous fluid directly to the end use target.

Furthermore it is characteristic for the method according to the invention that also other methods suitable for the dosing and transferring plastic masses and viscous fluids are suitable for use, and they are in accordance with the invention.

EXAMPLES 1 - 14

The used chemicals

The copolymers were prepared from ϵ -caprolactone monomer (ϵ -CL), > 99% purity, Fluka Chemika nr. 21510, lot 335334/ 1 794, and D,L-lactide (D,L-LA), Purac, lot DF 386H. As catalyst was used tin(II)octoate (Stannous 2-ethylhexanoate; SnOct), 95 % purity, Sigma nr. s-3252, lot 112H0248. As the initiator was used glycerol, 99,5% purity, Fluka BioChemika nr. 49767, lot 42489/2 1094.

The purification and storage of the used chemicals

In the used ϵ -caprolactone there was molecular sieves (adding date 15.02.1995), and the bottle was stored in a dark place at a temperature of 23 °C. The caprolactone was not
5 distilled again .

D,L-lactide was purified with recrystallization from toluene (b.p. 110 °C) using a mass ratio of 1:2 toluene/lactide. The lactide dissolved to a hot toluene was poured from round bottom flask to a decanter. The lactide solubilized to the toluene was let to recrystallize
10 overnight at 23 °C. After filtration the crystallized lactide was dried under reduced pressure for 4 days at +40 °C and 4 mbar. The same stages were repeated once. In the polymerizations was thus used twice recrystallized D,L-lactide which was stored in an exsiccator in a refrigerator at +4 °C. The tin octoate and the glycerol were used as such. They were stored in a dark place at +23 °C.

Preparations for polymerization

At preceding night the used lactide has been placed into a vacuum chamber at +40 °C and 4 mbar. The two-piece polymerization reactor (volume about 0,7 liter) was assembled, and
20 the condition of the Teflon gasket belonging to the reactor was checked. The proper closure of the upper part and the lower part of the reactor was ensured by a iron wire closing device. The male parts of the glass joints belonging to the reactor were wiped slightly with a vacuum grease.

Polymerization

The oil thermostat used for the reactor heating was regulated to 140 °C. The oil temperature varies during a polymerization within 5 °C above and below the set temperature. Lactide was weighed first about 10 g into a small decanter (accuracy 0,0001
30 g). On the lactide the tin octoate and the glycerol was weighed using a Pasteur pipet. After this the decanter was poured into the reactor, and the rest of the lactide was weighed with

another balance (accuracy 0,01 g) . ϵ -Caprolactone was then either poured or pipeted on lactide.

The magnetic agitator has been added to the reactor before the reactor halves were closed.

- 5 The reactor was placed into a thermostat, and the agitation was adjusted to the speed of 250 1/min. The reactor was flushed with Argon (AGA, grade S, 99,99%) for about 15 min. Argon was fed to the reactor through a glycerol trap. Finally the outside of the reactor was wrapped with a aluminium foil. When the forming copolymer started to become more viscous the agitation speed was adjusted again to the speed of 125 1/min.

10

The prepared copolymers and their analysis

- Table 1 summarizes the copolymerizations and their results using ϵ -caprolactone and D,L-lactide (ϵ -CL/D,L-LA). In all the polymerizations the temperature was 140 °C and the
15 polymerization time was 24 h (except in Example nr. 3 where it was 29 h). Molecular weights determined by gel permeation chromatography (GPC) are presented in Table 1 in terms of number average molecular weight Mn, weight average molecular weight Mw, and the polydispersity PD calculated as the ratio of the previous ones Mw/Mn. In the same
Table 1 there are also presented the transition temperatures of the polymerization products,
20 i.e.,melting temperature Tm and glass transition temperature Tg, determined using differential scanning calorimetry (DSC) .

GPC measurements

- 25 The GPC-samples for molecular weight measurements were prepared by dissolution of 15 mg of sample into 10 ml of chloroform. As columns were used columns of Polymer Laboratories Ltd with pore diameters of 100 - 10 000 Å. The used detector was RI-, i.e., refractive index detector, manufactured by Waters, and a 55 min run time with a flow rate of 1 ml/min were used. To determine the molecular weights of the samples were used
30 polystyrene (PS) standards manufactured by Polymer Laboratories, and the calibration curve based on the same. Because there is no experimental Mark-Houwink constants a and

K available, the molecular weights in the Table 1 are not absolute molecular weights for the samples but relative values in comparison with PS standards.

Table 1

Example	ϵ -CL D,L-LA- ratio (M-%)	SnOct- conc. mol/ mol Σ monomers	Glycerol conc. mol/ mol Σ monomers	GPC results			DSC results	
				M_n	M_w	PD	T_m	T_g
				(g/mol)	(g/mol)		(°C)	(°C)
1	100/0	0,0001	0,005	-	-	-	56	-
2	80/20	0,0001	0,005	35000	50000	1,4	47	-
3	80/20	0,0001	0,005	40000	60000	1,5	42	-
4	80/20	0,0001	0,005	40000	60000	1,5	45	-
5	80/20	0,0001	0,0005	165000	272000	1,65	46	-53
6	80/20	0,0001	0,25	-	-	-	-	-
7	100/0	0,0001	0,25	4300	5200	1,2	35	-
8	100/0	0,0001	0,05	445	729	1,6	-	-
9	100/0	0,0001	0,05	-	-	-	-	-
10	100/0	0,0001	0,25	2000	2600	1,3	-	-
11	100/0	0,0001	0,0125	-	-	-	53	-
12	100/0	0,0001	0,023	10000	12000	1,2	-	-
13	100/0	0,0001	0,034	-	-	-	43	-
14	80/20	0,0001	0,25	1100	1400	1,3	-	-

DSC measurements

In the DSC measurements the 5 - 10 mg sample was heated with a rate of 10 °C/min in a calorimeter chamber. In order to get a similar thermic history for all the samples, the samples were heated above their melting temperature to temperature of + 80 °C and cooled down to about -50 °C. The T_m and T_g values were determined from the curve recorded from the second heating, and they are presented in the Table 1. In Figure 4 is presented the DSC curve of the product prepared in Example 3, which is typical for all the polymers according to the invention.

Presentation of the characteristic monomer ratio-molecular weight dependence for ϵ -CL/D,L-LA copolymers

When the monomer ratio-molecular weight value pairs corresponding to the polymer products from Examples 1 - 14 (Table 1) and being suitable for implantation use are presented graphically in a right angle co-ordinate system, one can see that the hit points are located on the area between two curves (the shaded area in Figure 1). It is apparently possible to adjust the properties of the implant material according to the invention, of which melt viscosity, degradation rate in the body, and mechanical properties in a solid state are the most significant, by means of Figure 1 based on Examples 1-14 by selecting suitable combinations of comonomer ratio and polymerization parameters (of which the concentration of the so called initiator compound can be mentioned here). It is self-evident to anyone skilled in the art that the method to regulate material properties described in the invention can also be used with other monomer combinations suitable for the production of biodegradable implant materials.

EXAMPLES 15-26

Dependence between biodegradability and monomer composition of ϵ -CL/D,L-LA copolymers plasticizable in the range of temperatures from 37 to 55 °C

The biodegradability of typical materials prepared in the manner described above was tested by hydrolysis experiments in a buffered aqueous solution at a temperature of 37 °C (Examples 15 - 26; Table 2). The change of sample weight was followed with time so that their degradation rate was demonstrated. The hydrolytic degradation is the first, and thus the limiting, stage in regard to biodegradation, and therefore reflects quite well the overall total degradation rate in vivo, too. Based on experimental results Figure 2 illustrates the dependence between monomer composition and degradation rate in polymers according to the invention. Degradation rate of a polymer in certain conditions is affected not only by the composition and consequent differences in hydrophilic character but at least by the average molecular weight, and this is why also samples having the same composition may have different degradation rates. The values presented in Table 2 can be regarded as typical

examples for the materials according to the invention. Naturally they do not, however, represent the only possible property combinations of the implant materials produced with the method according to the invention.

5 **Table 2**

Example nr.	Composition ϵ -CL/lactide (M-%)	Molecular weight (g/mol)	Decomposition rate
15	0/100	10 000	1 d
16	10/90	10 000	2 d
17	10/90	30 000	1 week
18	20/80	10 000	2 d
19	20/80	30 000	2 weeks
20	40/60	10 000	3 d
21	40/60	50 000	1 month
22	60/40	10 000	5 d
23	60/40	80 000	6-10 months
24	80/20	20 000	3 weeks
25	80/20	300 000	1 year
26	100/0	80 000	over 1 year

Claims

1. A material for implantation to the body in connection with surgical, medical, dental or veterinary clinical practices, its matrix or binding agent, being biocompatible and biodegradable at a controlled rate, and containing a copolymer prepared from as such known monomers *which is characterized by the fact that* the melting temperature of the material is adjusted through the selection of the monomer composition and manufacturing parameters to be preferably within a range of 4 -18 °C, most preferably 6 - 12 °C, above the body temperature, and the material thus is in a molten state or as plasticized capable to be placed in its location where it solidifies to a solid plastic, a wax or a rubbery material.
2. An implant material described in claim 1 *characterized by the fact that* the material is comprised of structural units derived from organic hydroxy acids, and is a high molecular weight polymer having an average molecular weight adjustable with the parameters of the manufacturing process.
3. An implant material according to claim 1 *characterized by the fact that* the material is comprised of lactide and ϵ -caprolactone.
4. An implant material according to claim 1 *characterized by the fact that* the material is melting and plasticizing at a temperature within the range from 37 to 55 °C, most preferably within the range from 43 to 48 °C, and forms at a temperature within or above said temperature ranges a flowing mass or viscous fluid which is mouldable and which can be used to fill holes, spaces, fractures and cavities.
5. An implant material according to claim 1 *characterized by the fact that* there is a combined action by the preselections of the monomer composition and the average molecular weight controlled through an initiator compound that the melting temperature of the polymer is located on the shaded area in Figure 1.
6. An implant material according to claim 1 *characterized by the fact that* it is biodegradable in body conditions .

7. An implant material according to claim 1 *characterized by the fact that* its degradation rate can be from some days to several years, and get any value inbetween.

5 8. An implant material according to claim 1 *characterized by the fact that* it contains trimethyl carbonate.

9. A method to place an implant material according to claim 1 to the body *characterized by the fact that* the material plasticizable by raising its temperature in a controlled manner is
10 at said higher temperature mouldable by hand or by a tool, and injectable by using a device suitable for extrusion of plastic masses or viscous fluids which device can be a heated press or syringe.

10. A method according to the claim 9 *characterized by the fact that* said implant material
15 is at temperatures in the range from 2 to 20 °C higher than the body temperature a plastic mass or a viscous fluid, and it solidifies at the body temperature to form a solid plastic, a wax or a rubbery material.

11. A method according to the claim 9 *characterized by the fact that* the force for the
20 transfer of the implant material is produced by a piston moving in a heated cylinder.

12. A method described in claim 9 *characterized by the fact that* said implant material is comprised of a biodegradable polymer matrix blended with a drug, hormones, or other active ingredients, or solid fillers or reinforcing agents such as hydroxyapatite, bone
25 allografts or choral based material.

13. The use of an implant material according to the claim 1 and a method according to the claim 9 in surgical, medical, dental or veterinary treatments for implantation to the body, possibly in order to release drugs or other active ingredients, for placement of bioactive
30 composite materials, to treat bone defects, for other orthopaedic applications, for injections into soft tissues in connection with, for example, plastic surgery, and corresponding veterinary treatments.

AMENDED CLAIMS

[received by the International Bureau on 15 May 1998 (15.05.98);
original claims 1-13 replaced by amended claims 1-14 (3 pages)]

1. A method to produce materials for implantation to the body in connection with surgical, medical, dental or veterinary clinical practices, its matrix or binding agent which is biocompatible and biodegradable at a controlled rate, by copolymerizing at least two as such known monomers derived from hydroxy acids to a copolymer which in normal ambient and body temperatures is solid but which, utilizing the temperature dependence of the physical state of said copolymer, in a higher temperature is plasticizable and thus suitable to be molded or transferred to a target area where it by cooling rapidly solidifies back either to a tough plastic, a wax or a rubbery material characterized by that
- the used monomers, the ratio of their amounts in the reaction mixture, and the set of polymerization parameters, of which the so called initiator compound and its percentage in the mixture are among the most important ones, are so selected that macromolecular copolymers with physical state transition temperatures from solid to fluid are in the range from 37 °C to 55 °C, preferably in the range from 43 °C to 48 °C, and
 - the selection of the ratio of the comonomer amounts and the average molecular weight controlled by the polymerization parameters is done by means of a diagram where the points fixed by the possible value pairs of said variables in right angle coordination fall in the area between two curves which can be determined experimentally.
2. The method according to claim 1 wherein the area including the points in right angle coordination fixed by the possible comonomer ratio average molecular weight value pairs is bordered by two downwards opening curves which resemble parabolas.
3. The method according to claim 1 characterized by that
- transition temperatures at which the macromolecular copolymers prepared by the method change their physical state temporarily and reversibly from solid to fluid, in other words are plasticized, are preferably in the range from 4 °C to 18 °C, most preferably from 6 °C to 12 °C, higher than the normal body temperature, and
 - in said or any higher temperature the prepared copolymers can be transferred as fluid.
4. The method according to claim 1 wherein the used comonomers are lactide and ϵ -caprolactone.

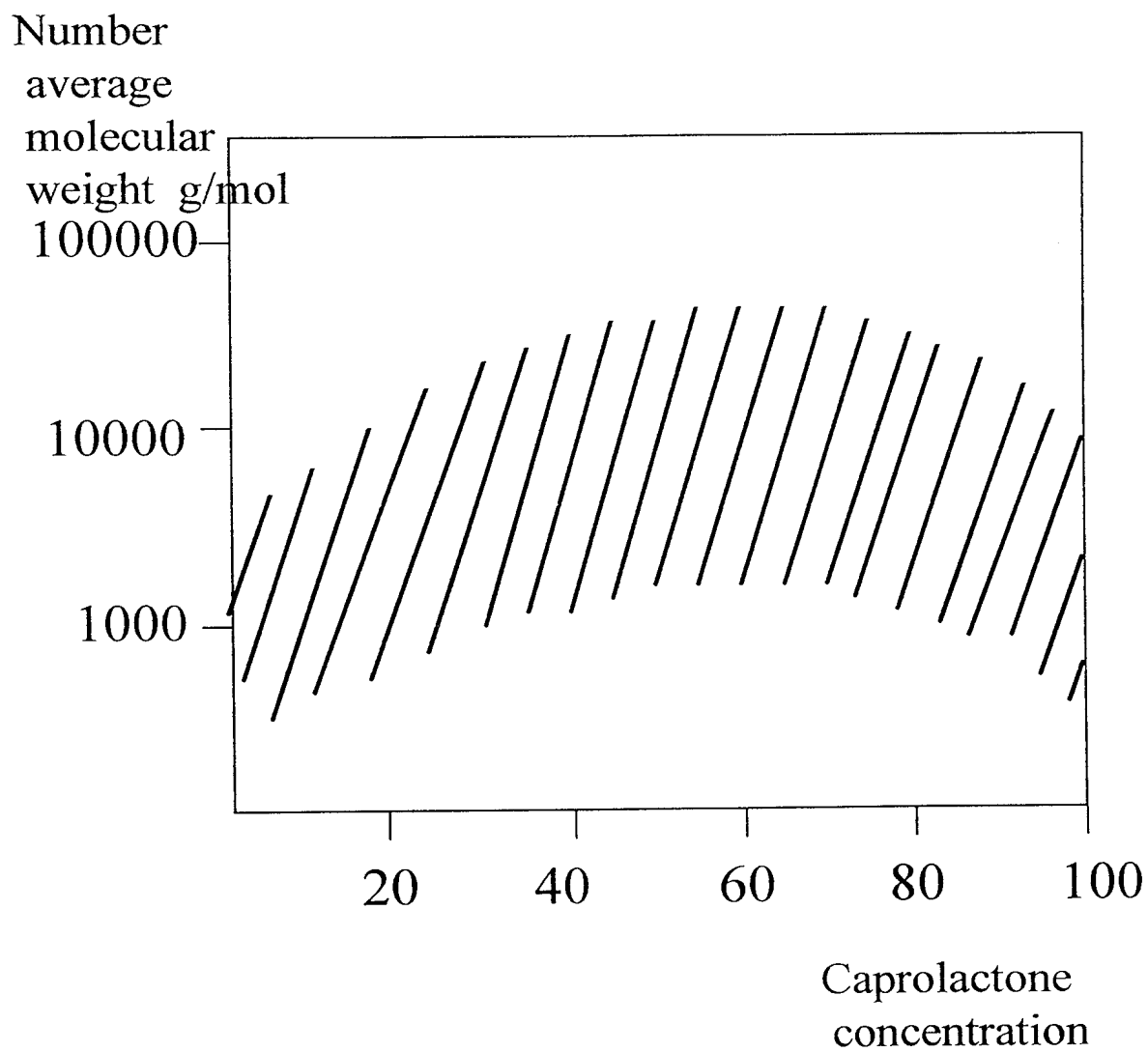
5. The method according to claim 1 wherein the control of the average molecular weight of the copolymer is done by selecting the reaction component called initiator compound and its percentage in the reaction mixture.
- 5 6. The method according to claim 1 wherein the so called initiator compound is 1,2,3-propanetriol, also known as glycerol, the catalyst of the reaction being tin(II) 2-ethylhexanoate, also known as stannous octoate, and the mole ratio of the amount of the initiator compound to the total amount of monomers is in the range from 0,0005 to 0,01.
- 10 7. The method according to claim 1 wherein the reaction mixture contains trimethyl carbonate, also known as 1.3-dioxane-2-one.
8. An implant material prepared according to claim 1 characterized by that the point in right angle coordination which is fixed by the selected comonomer composition and the
15 average molecular weight controlled by the selected method parameters falls on either of or between two experimentally determined, downwards opening parabolic curves.
9. The implant materials according to claim 8 characterized by that the area of points in right angle coordination fixed by the possible value pairs comonomer composition
20 versus average molecular weight is bordered by experimental curves which can be determined by preparing copolymers and analyzing their melting temperatures.
10. The implant materials according to claim 8 characterized by that they are plasticizable by raising their temperature in a controlled manner to a temperature in the
25 range from 2 °C to 20 °C higher than the body temperature to make them moldable by hand or by a tool or injectable by using a device suitable for extrusion of plastic masses or viscous fluids. and that at body temperatures they again solidifies to form a tough plastic, a wax or a rubbery material.
- 30 11. The implant materials according to claim 8 characterized by that they are plasticizing at a temperature in the range from 37 °C to 55 °C, preferably in the range from 43 °C to 48 °C, and form at temperatures within or above said temperature ranges flowing masses or viscous fluids which can be molded or used to fill holes, spaces, fractures or cavities when the force for the transfer of the implant material is produced by a piston
35 moving in a heated cylinder.
12. The implant materials claim 8 characterized by that they are biodegradable at a controlled rate in body conditions.

13. The implant materials according to claim 8 characterized by that their degradation rates in body conditions can be from some days to several years, and get any value between those limits.

5

14. The implant materials according to claim 8 characterized by that they are comprised of an at a controlled rate biodegradable polymer matrix blended with drugs, hormones, or other active ingredients, or solid fillers or reinforcing agents such as hydroxyapatite, bone allografts or choral based material.

1/4

**Fig. 1**

2/4

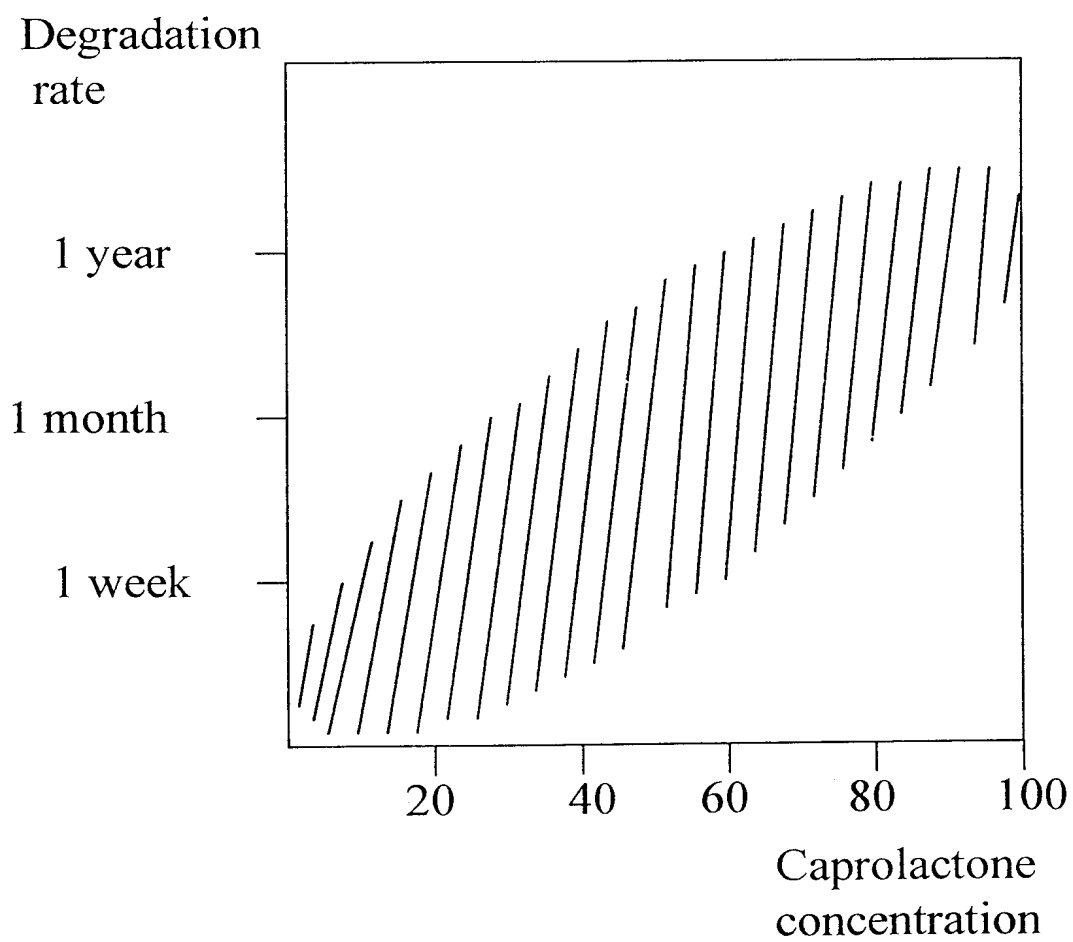
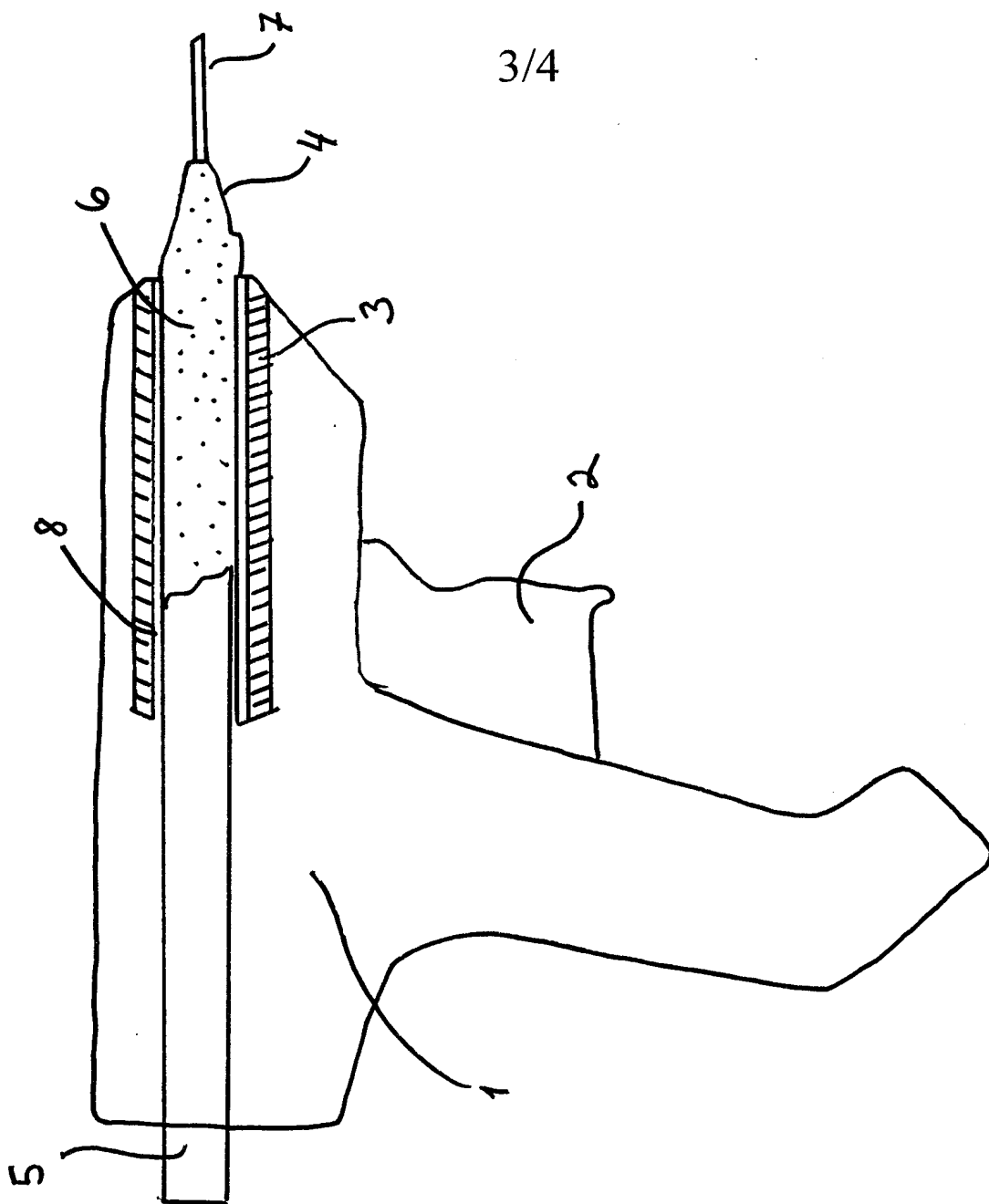


Fig.2



3/4

Fig. 3

4/4

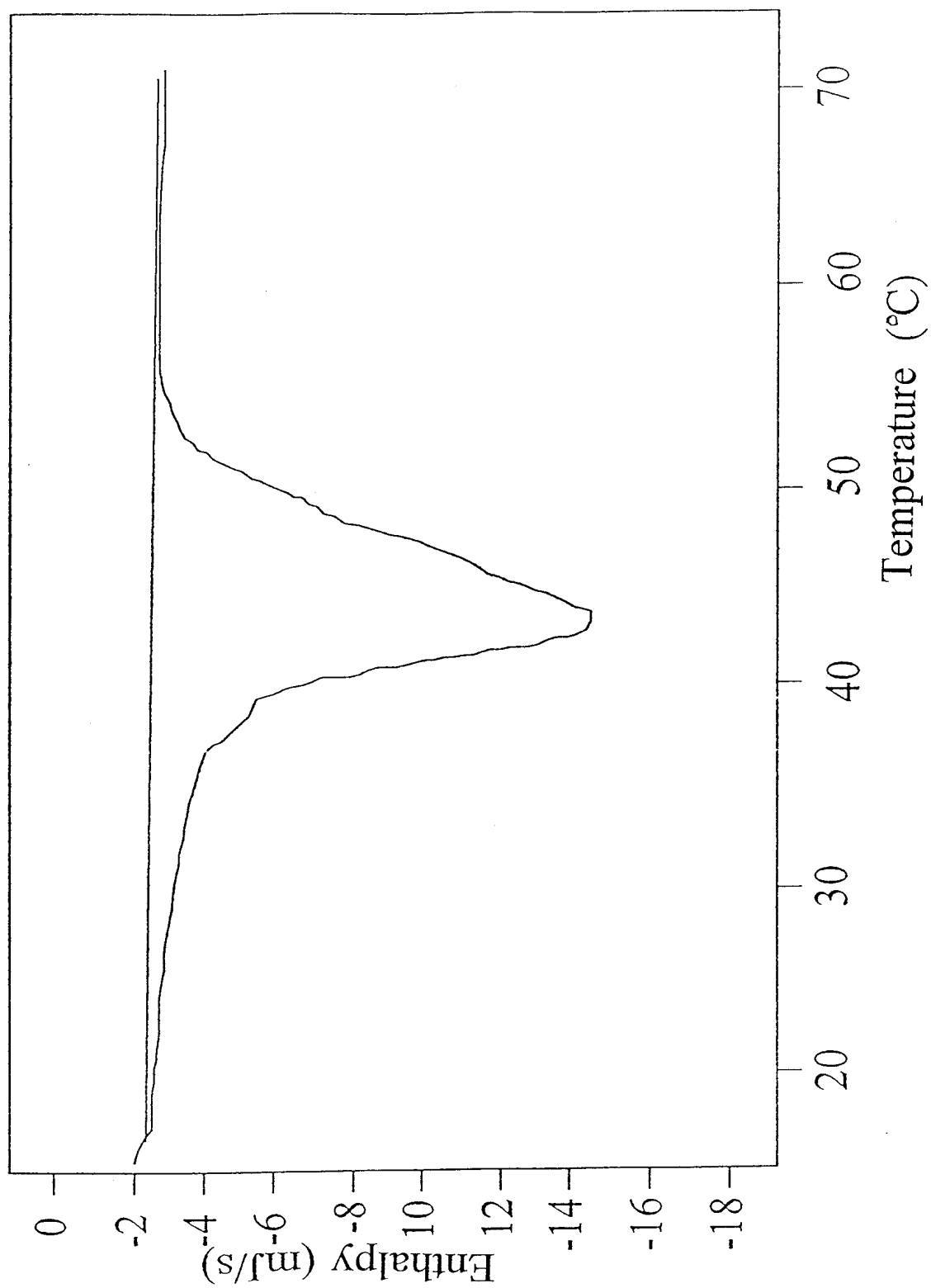


Fig. 4

INTERNATIONAL SEARCH REPORT

International application No.

PCT/FI 97/00786

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61L 31/00, A61L 27/00, A61K 6/087
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61L, A61F, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, CAPLUS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0747072 A2 (UNITED STATES SURGICAL CORPORATION), 11 December 1996 (11.12.96), column 3, line 42 - column 4, line 10; column 6, line 14-23 --	1-13
X	US 4595713 A (KENNETH ST. JOHN), 17 June 1986 (17.06.86), column 3, line 1 - line 19; column 6, line 3 - line 23; claims 1-3 and 8-10 --	1-13
A	EP 0628587 A2 (UNITED STATES SURGICAL CORPORATION), 14 December 1994 (14.12.94), claims -- -----	1-8

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

23 March 1998

Date of mailing of the international search report

26 -03- 1998

Name and mailing address of the ISA/
Swedish Patent Office
Box 5055, S-102 42 STOCKHOLM
Facsimile No. +46 8 666 02 86

Authorized officer

Sofia Nikolopoulou
Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.

PCT/FL/97/00786

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 9-13
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 9-13 relate to methods of treatment of the human or animal body by surgery or by therapy/diagnostic methods practised on the human or animal body/Rule 39.1.(iv).
Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

02/03/98

International application No.

PCT/FI 97/00786

Patent document cited in search report			Publication date	Patent family member(s)			Publication date
EP	0747072	A2	11/12/96	CA	2175285	A	08/12/96
				US	5641502	A	24/06/97
US	4595713	A	17/06/86	AU	578135	B	13/10/88
				AU	5353086	A	13/08/86
				EP	0210226	A	04/02/87
				JP	62501611	T	02/07/87
				WO	8604235	A	31/07/86
EP	0628587	A2	14/12/94	CA	2123647	A	12/12/94
				US	5543218	A	06/08/96